Simulation of reproductive risk and emergence of female reproductive cessation

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Abstract

Using a simple computer model for evolution, we show that in a sexual population subject only to age-increasing reproductive risk, a cessation of female reproduction emerges.

Key words: Population dynamics; Aging; Monte Carlo Simulations; Evolution; Menopause

1 Introduction

The significance of post-reproductive survival is one of most intriguing evolutionary unanswered questions related to reproduction and aging. A very important example of that is the human menopause. Despite of several theories proposed, the early female reproductive senescence, which has been also observed, although generally less clear-cut, in some other species, for instance, rats, macaques, lions, pilot whales, chimpanzees, elephants [1] remains one of the great puzzles of evolution theory.

In the specific case of humans, whether this postreproductive life is an adaptive consequence of natural selection, or is a non-adaptive artifact of the rapid increase in longevity over the past few centuries [2], many theories why the menopause evolved are based on unusual circumstances affecting the human life history (for review, see Ref.[3] and references therein). It has been suggested that menopause could act evolutionarily to protect the ageing woman from the hazards of childbirth. That is, as humans evolved and became able to reach greater ages, there came a point when survival during childbirth began

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to decline as a function of further ageing and increased frailty [4]. 'Premature' death of the mother would also put at risk any existing children and their potential for reproduction [5]. At the age when the risk of child-bearing outweighs the benefit of producing progeny, natural selection would favour women who became infertile; thus, the evolutionary pressure for menopause. A different theory is that the human menopause arises from the prolonged infant dependency on the mother, coupled with the risks of late pregnancy and child-bearing, due to the large neonatal brain size. An alternative theory is that menopause enhances fitness by producing post-reproductive grandmothers who can assist their adult daughters. Recently a theoretical model incorporating both of these theories has been sucessful in providing a possible evolutionary explanation of menopause [6].

Investigations of evolutionary problems by physicists have in fact boomed in the last few years. In particular, they have pioneered the use of techniques derived from the availability of powerful low-cost computers to fulfill the lack of and complement experimentation [8]. Since computer simulations of natural systems can provide much insight into their fundamental mechanisms, they can be used to test theoretical ideas that could be otherwise viewed as too vague to deserve the status of scientific knowledge [9]. Among the many computer models introduced to describe the evolution of populations [10], the Penna bit-string model [11], the Redfield model [14] and Stauffer model [15,18] have been stood out for predicting many phenomena in population dynamics.

The sexual version of the Penna model for mutation accumulation theory was first introduced by Bernardes [12], followed by Stauffer et al. [13] who adopted a slightly different strategy. We are going to describe the second one. The genome of each (diploid) organism is represented by two computer words. In each word, a bit set to 1 at a position ("*locus*") corresponds to a deleterious mutation - a "perfect" strand would be composed solely of zeros. The effect of this mutation may be felt by the individual at all ages equal to or above the numerical order of that locus in the world. As an example, a bit set to 1 at the second position of one of the bit-strings means that a harmful effect may become present in the life history of the organism to which it corresponds after it has lived for two time periods ("years"). In order to count the accumulated number of mutations and compare it with a specified threshold T, it is necessary to distinguish between recessive and dominant mutations. A mutation is counted if two bits set to 1 at the same position in both strings or if it appears in only one of the bit-strings but at a dominant position. The dominant positions are randomly chosen at the beginning of the simulation and are the same for all the individuals. Reproduction is modeled by the introduction of new genomes in the population. Each female and male becomes able to reproduce after having reached a minimum age, after which a female randomly chooses an able male to breed and it generates a fixed number of offspring at the completion of each period of life. To construct one offspring genome so, each

string of the mother genome is cut at a randomly selected position, the same for both strings, and the left part of one is combined with the right part of the other, thus generating two new combinations of the original genes. Finally, m_f deleterious mutations are randomly introduced, and then the selection of one of these completes the formation of the haploid gamete from the mother. The same process occurs with the male's genome, producing the male gamete with m_m deleterious mutations. These two resulting bit-string form the offspring genome. The gender of the newborn is then randomly selected, with equal probability for each sex.

The Redfield's model is an elegant model requiring much less computer time than the Penna model, but having no age structure. It is not a population dynamics model following the lifetime of each individual, but only simulates their probabilities to survive up to reproduction. In Redfield's program the population is characterized by a distribution of mutations $P(m)$, $m = 0, 1, ...$, giving the probability that an individual has m genetic diseases in the genome. Darwinian selection of the fittest then transforms this $P(m)$ into a survivor distribution $L(m) \propto (1-s)^m P(m)$ giving the probability that a survivor has m deleterious mutations in the genome, where $s = 0.1$ is a selection coefficient. In the sexual case n new hereditary mutations happen according to the Poisson distribution $\mu^n \exp(-\mu)/n!$, where $\mu \simeq 1$ corresponds to the mutation rate per genome per generation. In the sexual case, after selection transformed the progeny $P(m)$ distribution into the survivor distribution $L(m)$, mutations of a rate μ produce the female distribution $F(m)$ and those of a rate $\alpha\mu$ give the male distribution $M(m)$. Then male gametes (sperm cells) are produced containing half of the male genome; thus, their mutation number m_m is roughly half of the number of the number of mutations in the father's genome. Analogously, the number m_f of mutations in the female gametes (egg cells) is roughly half of the mother's number of mutations. The fusion of two gametes adds these two numbers, $m = m_m + m_f$, to produce the mutations in the progeny distribution $P(m)$. The cycle is repeated until changes in each distribution become negligible. In fact, the mutations in each gamete are not exactly half of the parent but follow a binomial distribution, which simulates the random selection of the transmitted half of the genome via the process of meiosis, crossover, and mitosis.

Of particular interest here is the Stauffer model, which although being a severe abstraction of biology, is particularly simple and had early successes in reproducing observed features of real populations, such as the Gompertz law [16], the catastrophic senescence of Pacific Salmon [17], the vanishing of cod in the northwest Atlantic through over-fishing [18], and the social needs of humans for a minimum population size [18].

The present work can represent a step in the direction of understanding more the evolutionary origin of menopause. In this way, the simulations reported

here test recent assumptions proposed in a work using the Penna model, in which menopause was found to self-organize from a combination of two effects: a reproductive risk of the mother that increases with the number of active mutations and thus with age; and child care, in the sense that young children die if their mother dies [19].

2 Model

In the sexual version of the Stauffer model [20], each individual of the population, which consists of males and females, is genetically represented by two integers, the minimum reproduction age a_m and the genetic death age a_d.

Individuals die with certainty if their age reaches a_d, and they die earlier with probability $V = N(t)/N_{max}$ at every iteration, where $N(t)$ is the actual population size and N_{max} a so-called carrying capacity of the environment taking into account the limitations of food and space (Verhulst factor). For computer simulations this logistic factor has the benefit of limiting the size of the population to be dealt with. At every time step and for each individual a random number between zero and 1 is generated and compared with V: if this number is smaller than V the individual dies, independently of its age and genetic death age a_d.

If the female succeeds in surviving until the minimum reproduction age a_m, it generates, with probability p_b, b offspring every iteration until death. The female randomly chooses a male to mate, with age also greater or equal to a_m. The offspring randomly inherits the a_m and a_d values from one of the parents, independently, apart from random changes (mutations) by ± 1. The sex of the baby is randomly chosen, each one with probability 50%. This procedure is repeated for each of the b offspring.

The probability $p_b(i)$ for individual i to get b children takes into account the well known (see e.g. [21]) trade-off between fecundity and longevity and is the lower the larger the difference $a_d - a_m$ is:

$$p_b(i) \propto 1/(a_d(i) - a_m(i))$$

where we require $0 \leq a_m < a_d \leq a_{max}$. We start our simulations with $a_m = 1$, $a_d = 16$ (or $a_d = 16$) and after thousand time steps the model shows an emergence of senescence and a typical age of death [15].

In order to simulate the evolution of populations with females subjected only to reproductive risk R, we now introduce the following ingredients in the model:

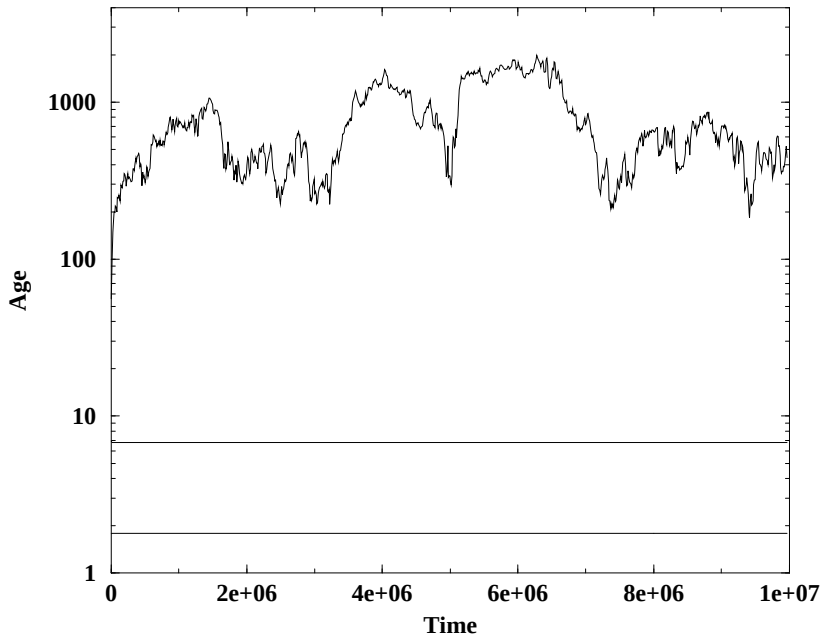

Fig. 1. Time evolution of the cessation of reproduction (menopause) age a_c (upper curve), the genetic death age a_d (middle curve) and the minimum reproduction age a_m (lower curve) for female population without reproductive risk. Logarithmic scales are used for the y axis (age).

- Reproductive Risk: At the moment of giving birth, we calculate the reproductive risk of a female to die. This is done through the expression:

$$Risk = \min\left[1, \frac{\beta * (a(i) - a_m(i))}{a_d(i) - a_m(i)}\right]$$

  where $a(i)$ is the actual female age and β is a predefined proportionality factor, which can reduce or increase the whole risk function. A random number between zero $r \in [0, 1]$ is drawn, and then the females dies if and only if $r < Risk$.
- Age of cessation of female reproduction a_c, introduced here as a new variable. In the usual model all individuals can reproduce at every period of life until death. Now, for females, we define a maximum age of reproduction a_c, which is equal to a_d at the beginning of the simulation. It means that - *only at the beginning of the simulation* - females can reproduce until the end of their lives (there is no menopause at the beginning). When a female with a given value of a_c gives birth to a daughter, the daughter's value of a_c is mutated randomly to $a_c \pm 1$.

3 Results

To obtain all curves presented here we simulated 20 different populations (samples) during $10,000,000$ time steps. The parameters of the simulations are:

- Initial population $= 30,000$ (half for each sex);
- Maximum population size $N_{max} = 1,500,000$;
- Number of offspring $b = 3$;

Simulations with less samples or shorter times sometimes gave misleading stability. In Figure 1, which corresponds to the standard results obtained using the original sexual Stauffer model without reproductive risk, we present the time evolution of the average value of the minimum age of reproduction a_m, the genetic death age a_d and the maximum age of reproduction a_c (top to bottom, respectively). From this figure we can observe that in order to maximize the probability p_b, which happens when the difference $(a_d - a_m)$ is minimized, a_d ($\overline{a_d} \simeq 6$) stays a value not much bigger than a_m ($\overline{a_m} \simeq 2$). If the death age a_d would evolve to a very large value when compared to the minimum age of reproduction a_m, then the probability to reproduce p_b would be very small, because p_b decreases for large $(a_d - a_m)$. As well, we also can see in this figure that the menopause age becomes bigger than the genetic death age, since a_d can not be greater than a_{max} and there isn't any restriction in the maximum value of a_c, in such a way that the maximum age of reproduction a_c is allowed to reach values bigger than the death age a_d. This means only that the females can reproduce until the end of their lifes, i.e., the reproductive cessation in females can not be observed in this old version without reproductive risk.

On the other hand, when the reproductive risk is introduced, as can be seen in Figure 2 (with $a_{max} = 1200$), the menopause age a_c stays below the death age a_d. From this result we can notice that there is a compromise between the lower reproductive risk $Risk$ and the probability to reproduce p_b, which is related to the value of the difference $(a_d - a_m)$: if $(a_d - a_m)$ reaches a small value, i.e., a_d not much bigger than a_m, a high reproduction rate dominates and a strong selection pressure caused by the high reproductive risk could drive the population to extinction. In this way, in order to soften the effects from the reproductive risk and to warrant the survival of the population, a_d evolves to values much bigger than a_m.

This particular feature that a_d plays in the model with or without reproductive risk have been obtained from simulations when two different maximum values a_{max} - the maximum value which a_d can reach in the simulation - were used. When we consider $a_{max} = 200$ (see Fig. 3) the difference $(a_d - a_m)$ is still big enough to produce a strong selection pressure against the females to warrant

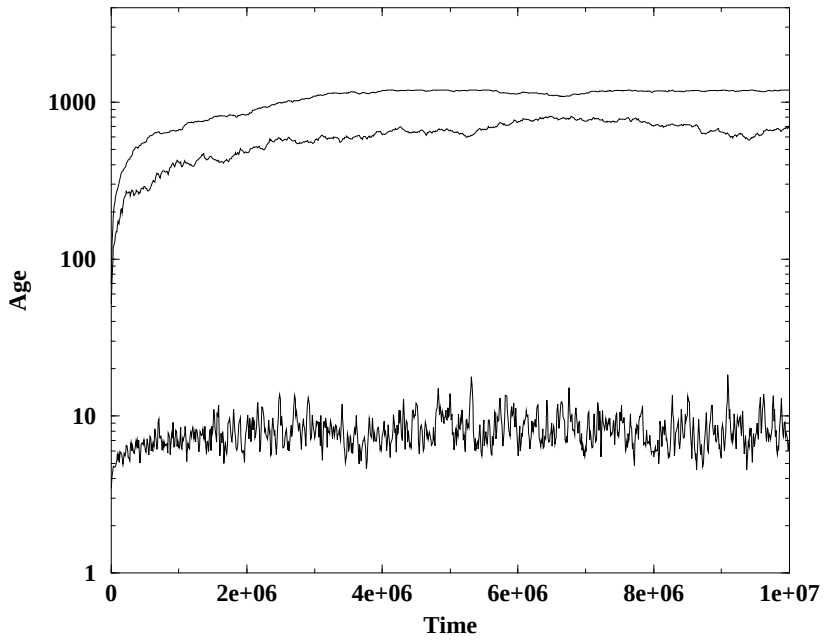

Fig. 2. Time evolution of the genetic death age a_d (upper curve), the cessation of reproduction (menopause) age (middle curve) and the minimum reproduction age (lower curve) for female population with reproductive risk using $\beta = 1.75$ and $a_{max} = 1200$. Logarithmic scales are user for the y axis (age).

the survival of the population. In other words, the high reproductive risk drives the females to remain reproducing as long as they live, it means that they will reproduce until the end of their lifes. However, if a_d is allowed to reach a very high value (see Fig. 2, where $a_{max} = 1200$), the opposite occurs and the cessation of reproduction of the females appears, since now the females do not suffer very strong effects from the reproductive risk due the large difference $(a_d - a_m)$. Given that the reproductive risk also increases with the age, it would seem to make sense for the females to cease reproducing at a certain age a_c below the death age a_d (but big enough to guarantee the survival of the population) in order to avoid completely the effects from the reproductive risk, since when the females stop to reproduce there will be no reproductive risk anymore.

The emergence of female menopause age obtained here (Fig. 2), using only a reproductive risk in giving birth that increases with age, was found with the Penna bit-string model [19] only when in addition to some kind of reproductive risk also maternal care was considered. Menopause was not observed in [19] for systems with only maternal care or with only reproductive risk. Furthermore, only 20% of the fertile female population had post-reproductive life and it was possible only when a very high period of maternal care was used,

which represented almost 24% of the maximum age of life in their simulations [19]. Their simulations had been performed under those restrictions suggested 40 years ago by Williams that menopause "may have arisen as a reproductive adaptation to a life-cycle characterized by senescence, unusual hazards in pregnancy and childbirth, and a long period of juvenile dependence" [4]. While the usual justification for the introduction of maternal care on the menopause restricts it to the human being, our simulations also to extend to other species, we don't take into account maternal care in our simulations, and nevertheless found menopause or analogs. The human being seems to be the only species to which kin assist in care and provisioning of young, since orphans regularly can survive even in adverse environments [7], our simulations suggest that this special human feature is not necessary for the emergence of menopause or analogs.

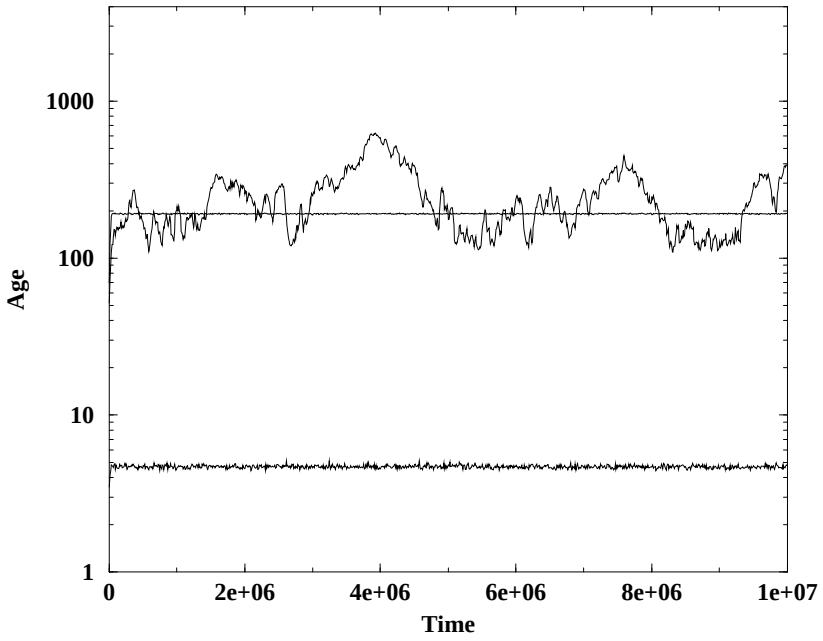

Fig. 3. Time evolution of the genetic death age (flat upper curve), the cessation of reproduction age (fluctuating curve) and the minimum reproduction age (lower curve) using $\beta = 1.75$ and $a_{max} = 200$. Logarithmic scales are user for the y axis (age).

Similar results have been also observed when using different functions for the reproductive risk, however in all cases simulated the emergence of menopause and its analogs depends on the suitable choice of parameters within the same model. Many simulations were performed in order to avoid to impose a maximum value for the death age, a_{max}, but without success: without this condition it was observed that the death age a_d evolves to a fixed value below the cessation age of reproduction a_c, which seems to drift towards infinity.

In addition, specifically concerning the constant β which can reduce or increase the whole risk function, we didn't manipulate it adequately in order to reproduce real problems related to the risks of childbearing the case of humans only. Instead, we had focused on the minimum value of β for which would be possible to notice the emergence of menopause using the simple Stauffer model. Different simulations were made, as it can be seen in Table 1, that show stationary values of a_m, a_d and a_c averaged over a prespecified number of time steps.

β	$\overline{a_m(i)}$	$\overline{a_d(i)}$	$a_c(i)$
0.00	1.79	6.80	$\rightsquigarrow \infty$
0.25	1.82	7.03	$\rightsquigarrow \infty$
0.50	1.85	7.33	$\rightsquigarrow \infty$
0.75	1.89	7.75	$\rightsquigarrow \infty$
1.00	1.95	8.34	$\rightsquigarrow \infty$
1.25	2.02	9.43	$\rightsquigarrow \infty$
1.50	2.15	11.88	$\rightsquigarrow \infty$
1.75	8.50	1182.81	633.69
2.00	11.18	1181.78	701.96
1.75	4.67	191.56	235.23

Table I. a_m, a_d and a_c averaged over the last time steps for different values of β and using $a_{max} = 1200$. In the last row, $a_{max} = 200$.

4 Conclusions

This paper reports on a simulation of populations under reproductive risk, in the framework of a simple model for biological aging. We show that a sexual population presents cessation of female reproduction as a functional characteristic of the system evolving under only reproductive risk. Thus simple explanations for menopause might be too simple since its existence in these simulations depends on the numerical values of model parameters.

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